REMARKS

Favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

I. CLAIM STATUS AND AMENDMENTS

Claims 1-13 and 17-30 were pending in this application when last examined.

Claims 17-20 and 29-30 were examined on the merits and stand rejected.

Claims 1-13 and 21-28 were withdrawn as non-elected subject matter. Applicants reserve the right to file a Continuation or Divisional Application on any cancelled subject matter.

Claims 29 and 30 are amended. Support for such amendments can be found on page 16 of the specification as filed.

No new matter has been added.

II. INFORMATION DISCLOSURE STATEMENTS

Applicants note that 1449 forms listing references were previously cited to the USPTO on January 13, 2006, July 18, 2006 and November 14, 2007. The Examiner is respectfully requested to return initialed copies of these forms with the next Office Action.

III. INDEFINITENESS REJECTIONS

On page 3 of the Office Action, claims 29 and 30 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for omitting essential steps.

Such claims have been amended to recite steps and therefore this rejection is overcome.

IV. ANTICIPATION/OBVIOUSNESS REJECTIONS

On pages 3-4 of the Office Action, claims 17-20, 29 and 30 were rejected under 35 U.S.C. § 102(b) as anticipated by Visser et al. Further, on pages 5-6, claims 17-20, 29 and 30 were rejected under 35 U.S.C. § 103(a) as obvious over Visser et al. in view of Coy et al. Applicants respectfully traverse these rejections.

The claimed invention relates to a conjugate of a substance P analogue and a chelator molecule. Said conjugate can be used for targeting and treating brain tumors. The conjugate of the claimed invention is labelled or unlabelled and has the structure of formula II (see claim 17) and the abbreviation

Chelator-R-Arg^1-Pro^2-Lys^3-Pro^4-Gln^5-Gln^6-Phe^7-Phe^8-Gly^9-Leu^{10}-X^{11}-NH_2,

wherein

R is $-CH_2-C(O)-$, $-CH(CO_2H)CH_2CH_2-C(O)-$ or $-CH(CO_2H)CH_2-C(O)-$ and

X is $Met(O_2)$, Met(O) or Ile;

or has the structure of an analogue of formula II with at least one of the modifications a)-f) in the amino acid sequence.

The conjugates of the claimed invention, which are based on substance P and analogues thereof with chelator DOTAGA, DOTASA or DOTA, are particularly useful for diagnostic investigations, as well as for therapeutic treatment of brain tumors. It was surprisingly found that the claimed radio-labelled conjugates are much more effective than DOTATOC, radio-labelled substance P, substance P analogues, saporin, or other small radio-labelled peptides with or without chelating agent in targeting and treatment of tumors, especially brain tumors, e,g, gliomas. It was also surprisingly found that metal complex formation was achieved quickly and that the claimed complexes possess a higher chemical stability, thus avoiding contamination of tissue or body fluids with free radio-nuclides. The substance P based radio-labelled conjugates show an unexpectedly high serum half-life time sufficient for application as internal radiodiagnostics and radio-therapeutics. Serum stability of the conjugates with substance P analogues is increased without decreasing the binding affinity to the neurokinine 1 receptor to an undesired extent. In some cases, the binding affinity is even improved when using the substance P analogues. It was also surprisingly found that the claimed substance P based radio-

labelled conjugates are capable of diffusing after administration and infiltrating tumor cell nests or satellite lesions, so that they can be detected and treated.

Another aspect of the claimed invention provides a method of targeting brain tumors, localizing or treating brain tumors and satellite lesions thereof in a host, in particular in humans, afflicted with brain tumor, by administrating to the host at least one of the conjugates of the claimed invention.

Visser et al. discloses a method for detecting and localizing tissues having neurokinine 1 receptors by administration of a composition comprising a labelled small peptide having a selective affinity to neurokinine 1 receptors. On page 4 of Visser et al., the general formula (I) for these labelled peptides is indicated, which is:

$$R^1\text{-}A^1{}_m\text{-}A^2{}_n\text{-}A^3{}_o\text{-}Pro_p\text{-}A^4{}_q\text{-}A^5\text{- Phe-}A^6\text{-}A^7\text{-}A^8\text{-}Met(O)_s\text{-}R^2$$

There are:

- nine options for R^1,
-three options for A^1,
- two options for A^2,
- two options for A^3,
- three options for A^4,
- six options for the combinations of m, n, o, p, and q,
- six options for A^5,
- two options for A^6,
- three options for A^7,
- two options for A^8,
- three options for s, and
- at least ten options for R^2,

amounting to several million different combinations. Thus, several million different compounds comprise formula (I).

On the other hand, the claimed invention encompasses only one of these millions of compounds (namely DOTA-Arg^1-Pro^2-Lys^3-Pro^4-Gln^5-Gln^6-Phe^7-Phe^8-Gly^9-Leu^{10}-Met(O)-NH_2), which is particularly well suited for the application at issue. In fact, as noted above, the claimed compound has surprising and unexpected properties not taught by the references.

A person skilled in the art cannot find any hint in Visser et al. that would make him or her select the claimed compound among the millions of others disclosed therein: The examples of Visser et al. only describe conjugates comprising DTPA as the chelator moiety, and there is no disclosure in the description that would lead to the above compound. Thus, even if the generic formula (I) of Visser et al. in theory includes the above compound (together with several million others), it fails to particularly teach the species claimed in the present invention. In other words, the claimed species cannot be at once envisioned from the disclosure of Visser et al. as required for a finding of obviousness.

Therefore, the subject-matter of the present invention is clearly novel in light of Visser et al.

Coy et al. relates to linear peptide analogues. This reference mentions that non-natural amino acids, such as Thienylalanine (Thi), are interchangeable with Phe.

However, since Visser et al. fails to teach all the other limitations of the present invention, combining the teachings of these references do not lead a person skilled in the art to the subject matter of claimed invention.

Therefore, the subject-matter of the present invention is also inventive.

Thus, for the above-noted reasons, these rejection are untenable and should be withdrawn.

CONCLUSION

In view of the foregoing amendments and remarks, it is respectfully submitted that the present application is in condition for allowance and early notice to that effect is hereby requested.

If the Examiner has any comments or proposals for expediting prosecution, please contact the undersigned attorney at the telephone number below.

Respectfully submitted,

Adrian MERLO et al.

/William R. Schmidt, II/

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